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 INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)



F5

<p>(51) Internationale Patentklassifikation ⁶ : A61K 31/415, C07D 405/04, 409/04</p>	A1	<p>(11) Internationale Veröffentlichungsnummer: WO 98/16223</p> <p>(43) Internationales Veröffentlichungsdatum: 23. April 1998 (23.04.98)</p>
<p>(21) Internationales Aktenzeichen: PCT/EP97/05381</p> <p>(22) Internationales Anmeldedatum: 1. Oktober 1997 (01.10.97)</p> <p>(30) Prioritätsdaten: 196 42 255.8 14. Oktober 1996 (14.10.96) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE).</p> <p>(72) Erfinder; und</p> <p>(75) Erfinder/Anmelder (nur für US): ROBYR, Chantal [CH/DE]; Bismarckstrasse 23, D-45470 Mülheim (DE). STRAUB, Alexander [DE/DE]; Moospfad 30, D-42113 Wuppertal (DE). NIEWÖHNER, Ulrich [DE/DE]; Gartenstrasse 3, D-42929 Wermelskirchen (DE). JAETSCH, Thomas [DE/DE]; Eintrachtstrasse 105, D-50668 Köln (DE). FEURER, Achim [DE/DE]; Schlinghofener Strasse 36, D-51519 Odenthal (DE). KAST, Raimund [DE/DE]; Badische Strasse 7, D-42389 Wuppertal (DE). STASCH, Johannes-Peter [DE/DE]; Alfred-Nobel-Strasse 109, D-42651 Solingen (DE). PERZBORN, Elisabeth [DE/DE]; Am Tescher Busch 13, D-42327 Wuppertal (DE). HÜTTER, Joachim [DE/DE]; Teschensudberger Strasse</p>	<p>13, D-42349 Wuppertal (DE). DEMBOWSKY, Klaus [DE/DE]; Bismarckstrasse 85, D-42115 Wuppertal (DE).</p> <p>(74) Gemeinsamer Vertreter: BAYER AKTIENGESELLSCHAFT; D-51368 Leverkusen (DE).</p> <p>(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Veröffentlicht Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</p>	
<p>(54) Title: USE OF CONDENSATED (HETARYL-SUBSTITUTED) 1-BENZAL-3-PYRAZOL DERIVATES FOR TREATING SPECIAL DISEASES OF THE CARDIOVASCULAR AND THE CENTRAL NERVOUS SYSTEMS</p> <p>(54) Bezeichnung: VERWENDUNG VON 1-BENZYL-3-(SUBSTITUIERTES-HETARYL)-KONDENSIERTEN PYRAZOL-DERIVATEN ZUR BELANDLUNG VON SPEZIELLEN ERKRANKUNGEN DES HERZ-KREISLAUFSYSTEMS UND DES ZENTRALNERVENSYSTEMS</p>		
<div style="position: absolute; left: 360px; top: 600px;"> R^2 R^3 R^4 CH_2 R^1 </div> <div style="position: absolute; left: 680px; top: 640px;">(I)</div>		
<p>(57) Abstract</p> <p>The present invention relates to the new application of condensated (hetaryl-substituted) 1-benzal-3-pyrazol derivatives of general formula (I), where R^1 to R^4 have the meanings given in the description, as drug products and new active substances, and more particularly to their use as vasodilators, possibly combined with organic nitrates and NO donors, possibly combined with compounds which inhibit the degradation of cGMP.</p>		
<p>(57) Zusammenfassung</p> <p>Die vorliegenden Erfindung betrifft die neue Verwendung von teilweise bekannten 1-Benzyl-3-(substituierten-hetaryl)-kondensierten Pyrazol-Derivaten der allgemeinen Formel (I), in welcher R^1 bis R^4 die in der Beschreibung angegebene Bedeutung haben, als Arzneimittel, neue Wirkstoffe, insbesondere ihre Verwendung als Vasodilatoren, gegebenenfalls in Kombination mit organischen Nitraten und NO-Donoren, und gegebenenfalls in Kombination mit Verbindungen, die den Abbau von cGMP inhibieren.</p>		

Le A 32079 = US 6180656



US006180656B1

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Fürstner et al.

(10) **Patent No.:** **US 6,180,656 B1**
(45) Date of Patent: **Jan. 30, 2001**

(54) **USE OF CONDENSATED (HETARYL-SUBSTITUTED) 1-BENZAL-3-PYRAZOL DERIVATES FOR TREATING SPECIAL DISEASES OF THE CARDIOVASCULAR AND THE CENTRAL NERVOUS SYSTEMS**

667345 8/1995 (EP) .

OTHER PUBLICATIONS

S.-M. Yu et al.: Inhibition of Platelet Function by A02131.1, a Novel Inhibitor. . . blood, vol. 87, No. 9, May 1, 1996, pp. 3758-3767.

C.-C Wu et al.: "YC-1 inhibited human platelet aggregation through. . . cyclase", British Journal of Pharmacology, vol. 116, No. 3, 1995, pp. 1973-1978.

F.-N. Ko et al. "YC-1, a Novel Activator of Platelet Guanylate Cyclase", Blood, vol. 84, No. 12, Dec. 15, 1994, pp. 4226-4233.

Primary Examiner—Raymond Henley, III

(74) *Attorney, Agent, or Firm*—Norris McLaughlin & Marcus P.A.

(75) **Inventors:** Chantal Fürstner, Ruhr; Alexander Straub, Wuppertal; Ulrich Niewöhner, Wermelskirchen; Thomas Jaetsch, Köln; Achim Feurer, Odenthal; Raimund Kast, Wuppertal; Johannes-Peter Stasch, Solingen; Elisabeth Perzborn, Wuppertal; Joachim Hütter, Wuppertal; Klaus Dembowsky, Schriesheim, all of (DE)

(73) **Assignee:** Bayer Aktiengesellschaft, Leverkusen (DE)

(*) **Notice:** Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

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(22) **PCT Filed:** Oct. 1, 1997

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§ 371 Date: Apr. 6, 1999

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(52) **U.S. Cl.** 514/406; 548/374.1

(58) **Field of Search** 548/374.1; 514/406

(56) **References Cited**

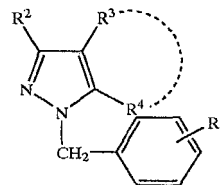
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470039 2/1992 (EP) .

(57) ABSTRACT

The present invention relates to the new use of 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivatives, some of which are known, of the general formula (I)

(I)



in which R¹ to R⁴ have the meaning indicated in the description, as medicaments, and to new active compounds, in particular to their use as vasodilators, if appropriate in combination with organic nitrates and NO donors and if appropriate in combination with compounds which inhibit the degradation of cGMP.

14 Claims, No Drawings

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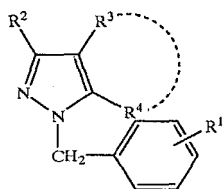
USE OF CONDENSATED (HETARYL-SUBSTITUTED) 1-BENZAL-3-PYRAZOL DERIVATES FOR TREATING SPECIAL DISEASES OF THE CARDIOVASCULAR AND THE CENTRAL NERVOUS SYSTEMS

This is a 371 of PCT/EP97/05381 filed Oct. 1, 1997.

The present invention relates to the new use of 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivatives, some of which are known, as medicaments, and to new active compounds, in particular to their use as vasodilators, if appropriate in combination with organic nitrates and NO donors and if appropriate in combination with compounds which inhibit the degradation of cGMP.

It is already known that 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivatives inhibit stimulated platelet aggregation in vitro (cf. EP-667 345 A1; C. -C. Wu et al., Br. J. Pharmacol. 1995; 116: 1973-1978; F. -N. Ko et al., Blood 1994; 84: 4226-4233; S. -U. Yu et al., Blood 1996, 87: 3758-3767).

It has now surprisingly been found that 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivatives of the general formula (I)

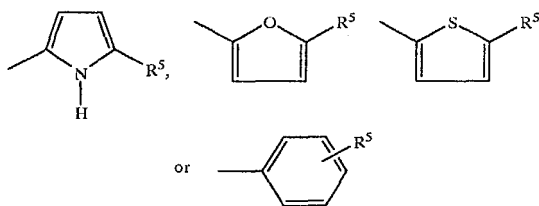


(I)

in which

R¹ represents hydrogen, halogen, hydroxyl or C₁-C₃-alkyl or C₁-C₃-alkoxy,

R² represents a radical of the formula



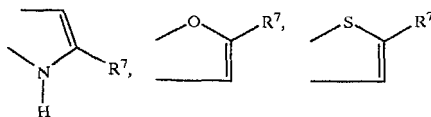
in which

R⁵ denotes hydrogen, halogen, carboxyl, C₁-C₃-alkyl, C₁-C₃-alkoxy carbonyl or a radical of the formula —CH₂—OR⁶,

in which

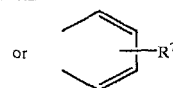
R⁶ denotes hydrogen or C₁-C₃-alkyl,

R³ and R⁴ together form a radical of the formula



2

-continued



in which

R⁷ denotes hydrogen, halogen, hydroxyl, C₁-C₃-alkyl or C₁-C₃-alkoxy,

and their isomeric forms and salts,

besides their weak antiaggregatory properties exhibit a marked vasodilatory action, in particular a lowering of blood pressure. They are thus suitable for the treatment of specific disorders of the cardiovascular system, in particular for the treatment of various forms of angina pectoris, of myocardial infarct, of cardiac insufficiency, of arteriosclerosis, stroke and of hypertension.

The compounds of the general formula (I) according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalene-disulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Physiologically acceptable salts can likewise be metal or ammonium salts of the compounds according to the invention if they have a free carboxyl group. Particularly preferred salts are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

In the context of the invention, C₁-C₃-alkyl represents a straight-chain or branched hydrocarbon radical having 1 to 3 carbon atoms. Examples which may be mentioned are: methyl, ethyl, propyl and isopropyl.

In the context of the invention, C₁-C₃-alkoxy represents a straight-chain or branched alkoxy radical having 1 to 3 carbon atoms. Examples which may be mentioned are: methoxy, ethoxy, propoxy and isopropoxy.

In the context of the invention, C₁-C₃-alkoxycarbonyl represents a straight-chain or branched alkoxycarbonyl radical having 1 to 3 carbon atoms. Examples which may be mentioned are: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and isopropoxycarbonyl.

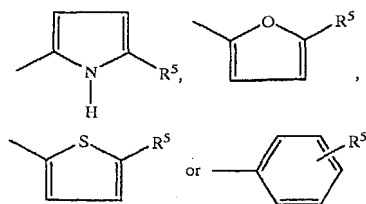
Preferably, compounds of the general formula (I) according to the invention

in which

R¹ represents hydrogen, fluorine, chlorine, C₁-C₃-alkyl or C₁-C₃-alkoxy,

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R^2 represents a radical of the formula



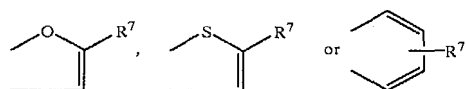
in which

R^5 denotes hydrogen, chlorine, carboxyl, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxycarbonyl or a radical of the formula $-CH_2-OR^6$,

in which

R^6 denotes hydrogen or methyl,

R^3 and R^4 together form a radical of the formula



in which

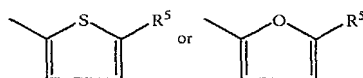
R^7 denotes hydrogen, fluorine, chlorine, C_1 - C_3 -alkyl or C_1 - C_3 -alkoxy, and their isomeric forms and salts, are used for the treatment of specific cardiovascular disorders.

Particularly preferably, compounds of the general formula (I) according to the invention

in which

R^1 represents hydrogen, fluorine, chlorine or methoxy,

R^2 represents a radical of the formula



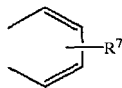
in which

R^5 denotes hydrogen, C_1 - C_3 -alkyl or a radical of the formula $-CH_2-OR^6$,

in which

R^6 denotes hydrogen or methyl,

R^3 and R^4 together form a radical of the formula



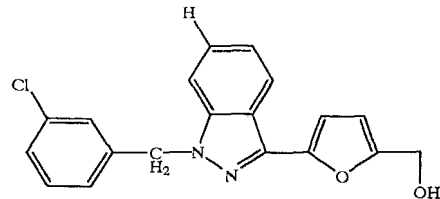
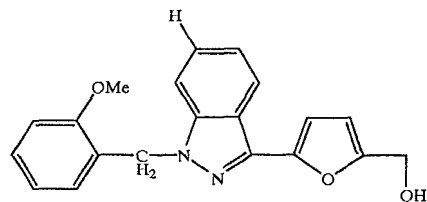
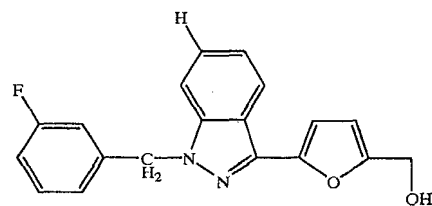
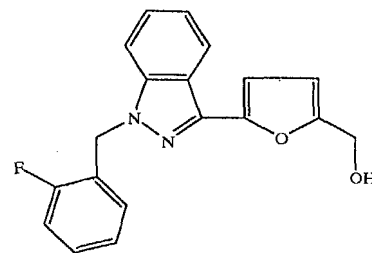
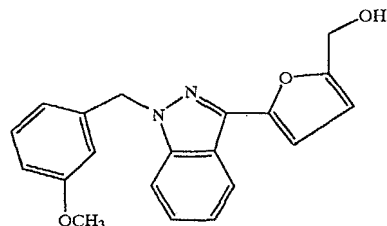
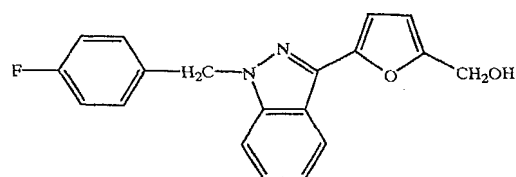
in which

R^7 denotes hydrogen, chlorine, fluorine, methyl or methoxy, and their isomeric forms and salts, are used for the treatment of specific cardiovascular disorders.

The invention additionally relates to new substances which are listed in the following table:

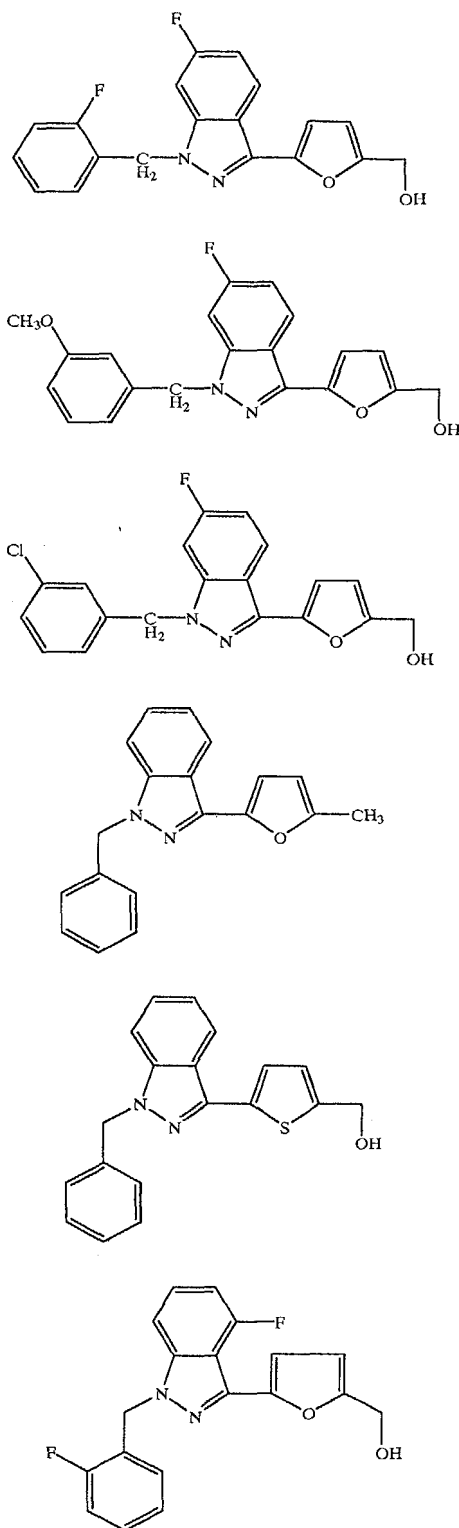
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TABLE



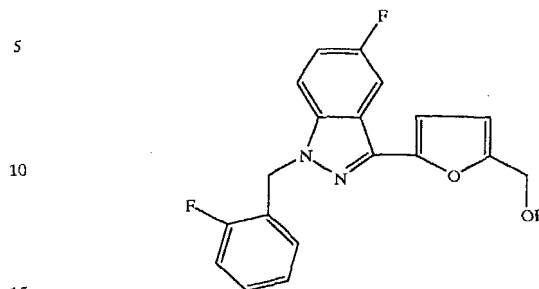
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TABLE-continued



6

TABLE-continued



The known and new compounds of the general formula (I) according to the invention can be prepared by customary methods, e.g. according to EP-667 345 A1.

Moreover, the invention preferably also includes the combination of the compounds of the general formula (I) according to the invention and of the new substances with organic nitrates and NO donors.

Organic nitrates and NO donors in the context of the invention are in general substances which display their therapeutic action via the release of NO or NO species. Sodium nitroprusside (SNP), nitroglycerine, isosorbide dinitrate, isosorbide mononitrate, molsidomine and SIN-1 and similar substances are preferred.

The invention additionally includes the combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP). These are in particular inhibitors of the phosphodiesterases 1, 2 and 5; nomenclature according to Beavo and Reifsnnyder (1990) TIPS 11 pp. 150-155. By means of these inhibitors, the action of the compounds according to the invention is potentiated and the desired pharmacological effect is increased.

The new and known compounds of the general formula (I) to be used according to the invention exhibit an unforeseeable, valuable spectrum of pharmacological action. They induce, for example, a vasorelaxation and lead to a lowering of blood pressure and increase in the coronary blood flow.

They are thus suitable for use in the treatment of specific disorders of the cardiovascular system such as, for example, the various forms of angina pectoris, of myocardial infarct, of cardiac insufficiency, of arteriosclerosis, stroke and of hypertension.

To determine the cardiovascular action, the following investigations were carried out: in vitro investigations on cells of vascular origin, the influence on guanylate cyclase-dependent cGMP formation was tested with and without NO donors. The vasorelaxant action was determined on rabbit aorta rings precontracted with phenylephrine. The hypotensive action was investigated in anaesthetized rats.

Stimulation of Soluble Guanylate Cyclase in Primary Endothelial Cells

Primary endothelial cells were isolated from pig aortas by treatment with collagenase soln. The cells were then cultured in culture medium until confluence was achieved. For the investigations, the cells were passaged, inoculated into cell culture plates and subcultured until confluence was achieved. To stimulate the endothelial guanylate cyclase, the culture medium was aspirated and the cells were washed once with Ringer's solution and incubated in stimulation buffer with or without NO donor (sodium nitroprusside, SNP, 1 μ M). Following this, the test substances (final

concentration 1 μ M) were then pipetted onto the cells. After the end of the incubation time of 10 minutes, the buffer solution was aspirated and the cells were lysed at -20° C. for 16 hours. The intracellular cGMP was then determined radioimmunologically.

TABLE A

Ex No.	% cGMP increase (NOSYNTH)
1	>1000
2	72
3	250
4	413
7	734
8	28
10	238
11	14
14 (YC-1)	>906
EP 667 345 Al	

Vasorelaxant Action in vitro

1.5 mm wide rings of an isolated rabbit aorta are placed individually under a pretension into 5 ml organ baths containing carbogen-aerated Krebs-Henseleit solution at a temperature of 37° C. The contractile force is amplified and digitalized, and recorded in parallel on a linear recorder. To generate a contraction, phenylephrine is added to the bath cumulatively in increasing concentration.

After several control cycles, the substance to be investigated is investigated in each further passage in increasing dose in each case and the contraction is compared with the height of the contraction achieved in the last previous passage. From this, the concentration is calculated which is necessary to reduce the height of the control value by 50% (IC_{50}). The standard administration volume is 5 μ l.

TABLE B

Ex. No.	Aorta IC_{50} (μ M)
1	4.1
3	16
4	9.2
14 (YC-1)	10
EP 667 345 A	

Blood Pressure Measurements on Anaesthetized Rats

Male Wistar rats having a body weight of 300–350 g are anaesthetized with thiopental (100 mg/kg i.p.). After tracheotomy, a catheter is inserted in the femoral artery for blood pressure measurement. The substances to be tested are administered orally in various doses as a suspension in Tylose solution by means of stomach tube.

TABLE C

Ex. No.	Dose	Max. blood pressure decrease	Time
1	10 mg/kg	–14 mm Hg	60 min
	30 mg/kg	–18 mm Hg	60 min
14 (YC-1)	10 mg/kg	–10 mm Hg	60 min
EP 667 345 Al	30 mg/kg	–18 mm Hg	60 min

The compounds described in the present invention are also active compounds for the control of illnesses in the central nervous system which are characterized by disorders of the NO/cGMP system. In particular, they are suitable for the elimination of cognitive deficits, for the improvement of learning and memory disorders and for the treatment of Alzheimer's disease. They are also suitable for the treatment of disorders of the central nervous system such as anxiety,

tension and depressive states, sexual dysfunctions and sleep disorders caused by the central nervous system, and for the regulation of pathological disorders in food, semi-luxury food and addictive drug intake.

Furthermore, these active compounds are also suitable for the regulation of the cerebral circulation and are thus effective agents for the control of migraine.

They are also suitable for the prophylaxis and control of the sequelae of cerebral infarcts (cerebral apoplexy) such as stroke, cerebral ischaemias and of cranio-cerebral trauma. The compounds according to the invention can likewise be employed for the control of states of pain.

The present invention includes pharmaceutical preparations which, besides non-toxic, inert pharmaceutically suitable excipients, contain one or more compounds according to the invention or which consist of one or more active compounds according to the invention, and processes for the production of these preparations.

The active compound(s) can optionally also be present in microencapsulated form in one or more of the excipients indicated above.

The therapeutically active compounds should be present in the abovementioned pharmaceutical preparations in a concentration of approximately 0.1 to 99.5, preferably of approximately 0.5 to 95% by weight of the total mixture.

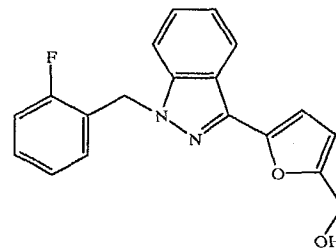
Apart from the compounds according to the invention, the pharmaceutical preparations mentioned above can also contain further pharmaceutical active compounds.

In general, it has proved advantageous both in human and in veterinary medicine to administer the active compound(s) according to the invention in total amounts of approximately 0.5 to approximately 500, preferably 5 to 100, mg/kg of body weight every 24 hours, if appropriate in the form of several individual doses, to achieve the desired results. An individual dose contains the active compound(s) according to the invention preferably in amounts of approximately 1 to approximately 80, in particular 3 to 30, mg/kg of body weight.

PREPARATION EXAMPLES

Example 1

1-(2-Fluorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole



0.8 g (2.5 mmol) of 1-(2-fluorobenzyl)-3-(5-formyl-2-furanyl)-indazole is suspended in 40 ml of propanol and 0.8 g of $NaBH_4$ is added slowly at 0° C. After stirring at room temperature for 1 hour, the clear solution is added to water, the mixture is extracted with ethyl acetate, the organic phase is dried with sodium sulphate and evaporated in vacuo, and the residue is chromatographed on silica gel using, toluene/ethyl acetate mixtures as eluent.

620 mg (77% of theory) of crystals are obtained.

M.p. (melting point): 83° C.

R_f (SiO_2 , toluene/ethyl acetate 2:1): 0.50

The examples in Tables 1, 2 and 3 were prepared analogously:

TABLE 1

Ex. No.	Structure	M.p. ¹⁾ °C.
2		95
3		82

¹⁾ Melting point

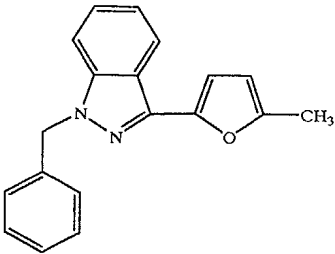
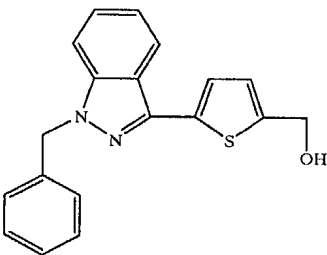
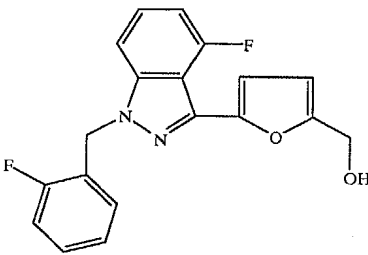
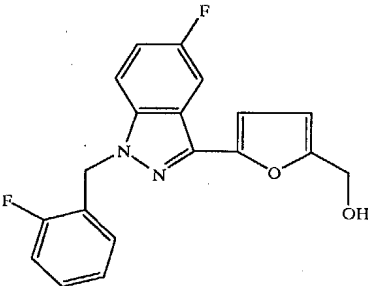
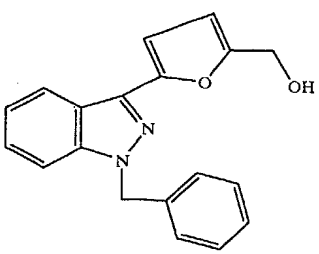
TABLE 2

Ex. No.	R ⁸	R ⁹	Yield (% of theory)	R _f	M.p. °C.
4		H	43 112	0.50 (TEA 1:1)	
5		H	50 109		
6		H	6		

TABLE 2-continued

Ex. No.	R ⁸	R ⁹	Yield (% of theory)	R _f	M.p. °C.
7		F	65		
8		F	40 95		
9		F	9		

TABLE 3

Ex. No.	Structure	Yield (% of theory) R_f	M.p. ° C.
10		92 63	0.40 (H:EA 3:1)
11			
12		89 136	0.33 (H:EA 1:1)
13		83 141	0.44 (H:EA 1:1)
14		112	

YC-1 (EP 667345A1)

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What is claimed is:

1. A compound selected from the group consisting of:

- 1-(2-fluorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole,
 1-(4-fluorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole,
 3-(5-hydroxymethylfuran-2-yl)-1-(3-methoxybenzyl)-indazole,
 1-(3-fluorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole,
 3-(5-hydroxymethylfuran-2-yl)-1-(2-methoxybenzyl)-indazole,
 1-(3-chlorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole,
 6-fluoro-1-(2-fluorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole,
 6-fluoro-3-(5-hydroxymethylfuran-2-yl)-1-(3-methoxybenzyl)-indazole,
 1-(3-chlorobenzyl)-6-fluoro-3-(5-hydroxymethylfuran-2-yl)-indazole,
 1-benzyl-3-(5-methylfuran-2-yl)-indazole,
 1-benzyl-3-(5-hydroxymethylthiophene-2-yl)-indazole,
 4-fluoro-1-(2-fluorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole and
 5-fluoro-1-(2-fluorobenzyl)-3-(5-hydroxymethylfuran-2-yl)-indazole.

2. A pharmaceutical composition comprising at least one compound according to claim 1, or an isomer or a salt thereof and a pharmaceutically acceptable carrier.

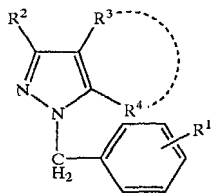
3. A process of preparing the pharmaceutical composition according to claim 2 comprising combining said at least one compound or an isomer or a salt thereof and a pharmaceutically acceptable carrier.

4. Method for treatment of a cardiovascular disorder, said method comprising administering to a patient in need thereof an effective amount therefor of at least one compound according to claim 1 or an isomer or a salt thereof.

5. The method according to claim 4 wherein said cardiovascular disease is hypertension.

6. Method for treatment of a central nervous system disorder, said method comprising administering to a patient in need thereof an effective amount therefor of at least one compound according to claim 1 or an isomer or a salt thereof.

7. A pharmaceutical composition comprising at least one 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivative of the general formula (I)

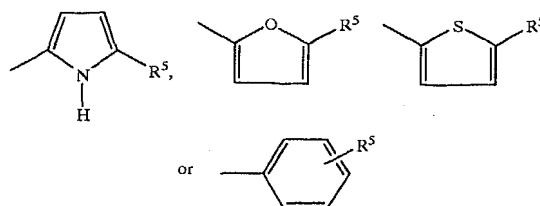


in which

R¹ represents hydrogen, halogen, hydroxyl or C₁-C₃-alkyl or C₁-C₃-alkoxy,

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R² represents a radical of the formula



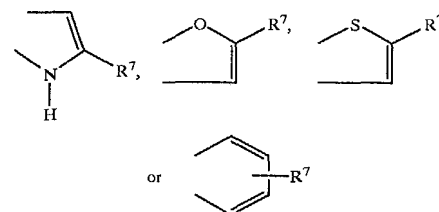
in which

R⁵ denotes hydrogen, halogen, carboxyl, C₁-C₃-alkyl, C₁-C₃-alkoxy carbonyl or a radical of the formula —CH₂—OR⁶,

in which

R⁶ denotes hydrogen or C₁-C₃-alkyl,

R³ and R⁴ together form a radical of the formula



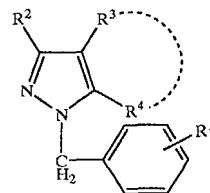
in which

R₇ denotes hydrogen, halogen, hydroxyl, C₁-C₃-alkyl or C₁-C₃-alkoxy,

or an isomer or a salt thereof, organic nitrates and NO donors.

8. A pharmaceutical composition comprising at least one 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivative of the general formula (I)

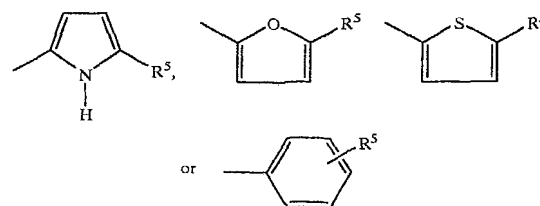
(I)



in which

R¹ represents hydrogen, halogen, hydroxyl or C₁-C₃-alkyl or C₁-C₃-alkoxy,

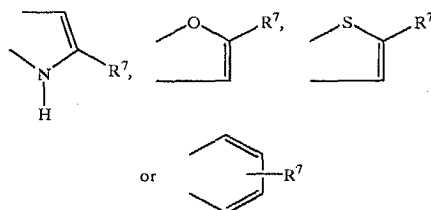
R² represents a radical of the formula



in which

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R^5 denotes hydrogen, halogen, carboxyl, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy carbonyl or a radical of the formula $-\text{CH}_2-\text{OR}^6$,
 in which
 R^6 denotes hydrogen or C_1 - C_3 -alkyl,
 R^3 and R^4 together form a radical of the formula

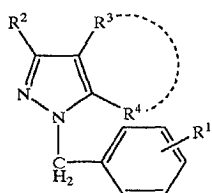


in which
 R_7 denotes hydrogen, halogen, hydroxyl, C_1 - C_3 -alkyl or C_1 - C_3 -alkoxy,
 or an isomer or a salt thereof and compounds which inhibit the degradation of cGMP.

9. A process of preparing the pharmaceutical composition according to claim 7 comprising combining said at least one 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivative, organic nitrates and NO donors.

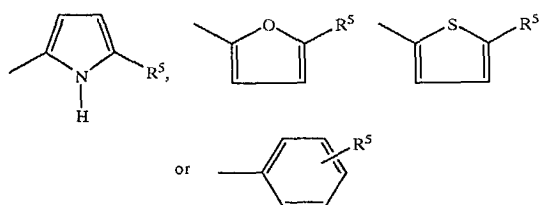
10. A process of preparing the pharmaceutical composition according to claim 8 comprising combining said at least one 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivative and compounds which inhibit the degradation of cGMP and a pharmaceutically acceptable carrier.

11. Method for treatment of a cardiovascular disorder, said method comprising administering to a patient in need thereof an effective amount thereof of at least one 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivative of the general formula (I)



in which

R^1 represents hydrogen, halogen, hydroxyl or C_1 - C_3 -alkyl or C_1 - C_3 -alkoxy,
 R^2 represents a radical of the formula

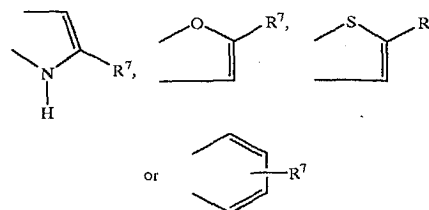


in which

R^5 denotes hydrogen, halogen, carboxyl, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy carbonyl or a radical of the formula $-\text{CH}_2-\text{OR}^6$,
 in which

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in which
 R^6 denotes hydrogen or C_1 - C_3 -alkyl,
 R^3 and R^4 together form a radical of the formula



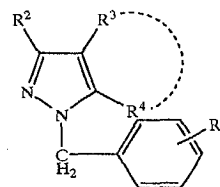
in which

R_7 denotes hydrogen, halogen, hydroxyl, C_1 - C_3 -alkyl or C_1 - C_3 -alkoxy,

or an isomer or a salt thereof.

12. The method according to claim 11 wherein said cardiovascular disease is hypertension.

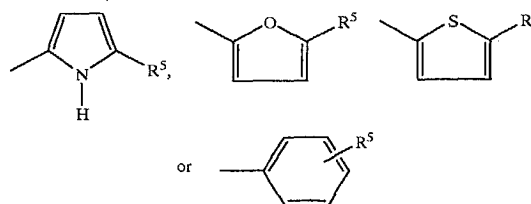
13. Method for treatment of a central nervous system disorder, said method comprising administering to a patient in need thereof an effective amount thereof of at least one 1-benzyl-3-(substituted hetaryl)-fused pyrazole derivative of the general formula (I)



in which

R^1 represents hydrogen, halogen, hydroxyl or C_1 - C_3 -alkyl or C_1 - C_3 -alkoxy,

R^2 represents a radical of the formula



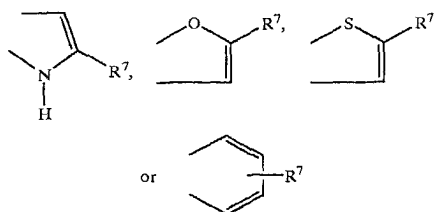
in which

R^5 denotes hydrogen, halogen, carboxyl, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy carbonyl or a radical of the formula $-\text{CH}_2-\text{OR}^6$,
 in which

R^6 denotes hydrogen or C_1 - C_3 -alkyl,

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R^3 and R^4 together form a radical of the formula



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in which

R^7 denotes hydrogen, halogen, hydroxyl, C_1 - C_3 -alkyl or C_1 - C_3 alkoxy,

5 or an isomer or a salt thereof.

14. The method according to claim 13 wherein said
10 central nervous system disorder is a cerebral infarct.

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